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Factor XIII deficiency: a rare cause of repeated abortions

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ABSTRACT

Factor XIII deficiency is a rare cause of early abortion. The obstetrical outcome of four pregnancies in two women with factor XIII deficiency is reported. Both women were treated with substitution therapy using locally-prepared cryoprecipitate. The outcome in these two women demonstrated the need for substitution therapy in early pregnancy leading to an increased chance of obstetrical success.

Keywords: bleeding disorders, factor XIII deficiency, pregnancy, repeated abortions

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INTRODUCTION

Factor XIII, the last enzyme in the clotting cascade, catalyses the covalent cross-linking of fibrin molecules. It converts the loose fibrin polymer into an organised cross-linked structure with increased tensile strength and makes it relatively resistant to fibrinolysis. Deficiency of factor XIII is inherited as an autosomal recessive disorder and is associated with various bleeding manifestations. Women with factor XIII deficiency have recurrent abortions and in men, it is associated with oligospermia and aspermia[1]. We report the obstetrical outcome of four pregnancies in two women with factor XIII deficiency.

CASE 1

A 29-year-old woman presented with a history of seven first trimester abortions. Her menstrual cycles were normal with average flow. She gave a past history of excessive bleeding requiring blood transfusion following a tooth extraction, and a history of excessive bleeding following a cut on the toe. There was no history of excessive bleeding from the umbilical cord at birth. She was a child of a consanguineous marriage, as her parents were first cousins.

Investigations, which included coagulation profile, thyroid profile, karyotyping and hysterogram, were normal. In view of a normal coagulation profile, repeated abortions and a history of excessive bleeding, urea solubility test for factor XIII deficiency was done and it was positive. She was given one unit of cryoprecipitate every month. One year later, she successfully conceived and the frequency of cryoprecipitate infusion was increased to one unit every fortnight. At eleven weeks of gestation, ultrasonography revealed a missed abortion. An evacuation was done after infusing one unit of cryoprecipitate.

She reported to the antenatal clinic six months later, at six weeks of gestation. Based on the outcome of the previous pregnancy, the dosage of cryoprecipitate was increased to two units every fortnight. The antenatal period was uneventful. At 38 weeks of gestation, labour was induced with intracervical PGE_2 gel and augmented with oxytocin and artificial rupture of membranes. She was given two units of cryoprecipitate during active labour. The course of labour was uneventful and she delivered a live female baby weighing 2890g. Post-partum, she had a persistent ooze from the uterine cavity which was controlled after infusing one unit of cryoprecipitate. The child did not have excessive bleeding from the umbilical stump. The episiotomy healed well, and the mother and the baby were discharged on the fifth postnatal day.

CASE 2

A 22-year-old woman (G_3 A^2) presented to our emergency unit with bleeding per vaginum at five weeks of gestation. The previous two abortions were in the first trimester. She was detected to have factor XIII deficiency at the age of seven years when she developed excessive bleeding from an injury to the tongue, following a fall. At birth, she had excessive bleeding from the umbilical cord for which blood transfusion was given. She was a child of consanguineous marriage and her sister was also detected to have factor XIII deficiency. There was a history of infertility in the family. Her two maternal uncles do not have children. The cause for the infertility is not known as they have not been investigated.

On examination, her general condition was stable. Abdominal ultrasonography showed a regular intrauterine gestational sac of five weeks size and the

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Table I. Classification of the three types of factor XIII deficiency.

	Factor XIII activity	Sub unit B	Sub unit A
Type I	Low	Absent or low	Absent or low
Type II	Low	Normal or near normal	Absent or very low
Type III	Low	Absent	Low

internal os was closed. In the course of hospital stay, she continued to have spotting per vaginum and the β hCG showed a declining value. An evacuation was done under cover of two units of cryoprecipitate. She was advised to start cryoprecipitate infusion prior to conception.

Five months later, she presented to our emergency department at eight weeks of gestation with bleeding per vaginum. She had not received cryoprecipitate in the periconceptional period. Physical examination revealed pallor (Hb was 3.8 g/dL). Vaginal examination revealed an eight week size uterus, with products of conception protruding through the os. Under cover of cryoprecipitate (4 units) and blood transfusion, evacuation of the products of conception was done.

DISCUSSION

Factor XIII is a zymogen found in plasma and platelets. In plasma, it is in the form of a tetrameric complex of two polypeptides sub unit A & B (A_2B_2) and in the platelets it is in the form of a dimer (A_2). Factor XIII deficiency has been classified into three types[2] (Table I). The symptoms vary depending on the type. In type I, only mild haemorrhagic symptoms may be seen. In type II, the characteristic finding is bleeding from the umbilical cord and in 25% of cases, intracranial haemorrhage has been reported[3]. Women with type II deficiency have a better chance of successful obstetrical outcome when put on prophylactic therapy. Post-partum haemorrhage has been reported with type III deficiency[4].

During pregnancy, factor XIII is found within the placenta. Factor XIII serves as an adhesive protein during the invasion of the endometrium by the cytotrophoblast and is essential just after 4-5 weeks of gestation[5]. When the concentration of factor XIII A in the placental bed is low, the cytotrophoplastic shell does not form adequately and results in an increased risk of abortion[6]. Successful outcome of pregnancy has been reported in women with factor XIII deficiency who were given substitution therapy with either factor XIII concentrate or fresh frozen plasma[7,8]. We used locally-prepared cryoprecipitate for substitution therapy. The ideal dose, interval of administration and type of factor XIII replacement required during pregnancy is not exactly known but a normal outcome has been reported when the level of factor XIII was maintained at approximately 3%[7]. In our cases, the factor XIII levels were not monitored. In the first case, based on the outcome of the eighth pregnancy, the dose of cryoprecipitate was increased in the subsequent pregnancy and that pregnancy had a favorable outcome.

Factor XIII deficiency is known to cause early abortions and has to be ruled out in a woman who has unexplained repeated first trimester abortions. The outcome in these two women demonstrates the need for substitution therapy in early pregnancy and also increases the chances of having a successful obstetrical outcome with substitution therapy in women with factor XIII deficiency.

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